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(54) **Title:** GENE EXPRESSION SYSTEMS AND RECOMBINANT CELL LINES

(57) **Abstract:** The present invention provides gene expression systems useful for detecting agonists of Toll-like receptors. The gene expression systems include a nucleic acid sequence encoding a Toll-like receptor and a second nucleic acid sequence that encodes a reporter operably linked to an expression control sequence. The recombinant cell lines include a gene expression system according to the present invention.

GENE EXPRESSION SYSTEMS AND RECOMBINANT CELL LINES

Background of the Invention

Cells of the immune system secrete a diverse set of compounds including cytokines, chemokines, co-stimulatory markers, and defensins in response to an immunological challenge.

Certain compounds known as immune response modifiers ("IRMs") possess potent immunostimulating activity including but not limited to antiviral and antitumor activity. Certain IRMs effect their immunostimulatory activity by, e.g., inducing the production and secretion of certain cytokines while inhibiting production and secretion of other cytokines. Certain IRMs are small organic molecules such as those disclosed in, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,352,784; 5,389,640; 5,482,936; 5,494,916; 6,110,929; 6,194,425; 4,988,815; 5,175,296; 5,367,076; 5,395,937; 5,693,811; 5,741,908; 5,238,944; 5,939,090; 6,245,776; 6,039,969; 6,083,969; 6,245,776; 6,331,539; and 6,376,669; and PCT Publications WO 00/76505; WO 00/76518; WO 02/46188, WO 02/ 46189; WO 02/46190; WO 02/46191; WO 02/46192; WO 02/46193; and WO 02/46194.

Additional small molecule IRMs include purine derivatives (such as those described in U.S. Patent Nos. 6,376,50 and 6,028,076), small heterocyclic compounds (such as those described in U.S. Patent No. 6,329,381), and amide derivatives (such as those described in U.S. Patent No. 6,069,149).

Other IRMs include large biological molecules such as oligonucleotide sequences. Some IRM oligonucleotide sequences contain cytosine-guanine dinucleotides (CpG) and are described, for example, in U.S. Patent Nos. 6,1994,388; 6,207,646; 6,239,116; 6,339,068; and 6,406,705. Other IRM nucleotide sequences lack CpG and are described, for example, in International Patent Publication No. WO 00/75304.

Some of these IRMs induce cellular responses (e.g., the production and/or secretion of cytokines, chemokines, etc.) through one or more Toll-like receptors (TLRs). For example, certain small organic molecule IRMs are agonists of one or more of TLR-1, TLR-2, TLR-4, TLR-6, TLR-7, and TLR-8. Additionally, CpG has been reported to act through TLR 9.

In certain cells of the immune system, TLR activation can be associated with activation of the transcription factor NF-κB. NF-κB activation is associated with certain cellular responses to an immunological challenge, such as the production and secretion of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1, and MCP-1. IRM induction of such cellular responses can be demonstrated by measuring activation of the transcription factor NF-κB in response to exposing a cell to an IRM compound (See, e.g., Chuang *et al.*, *Journ. of Leuk. Biol.*, vol. 71, pp. 538-544 (2002), and Hemmi *et al.*, *Nature Immunology*, vol. 3(2), pp. 196-200 (2002)). Thus, NF-κB activation can be used as a reporter of TLR activation. However, the extent of NF-κB activation does not necessarily correlate with the extent of the downstream cellular response. This is so because the downstream cellular response may be modulated by one or more additional factors.

Summary of the Invention

The present invention provides an expression system that includes a first nucleic acid sequence that encodes a Toll-like receptor operably linked to a first expression control sequence; and a second nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter. In some embodiments, the first nucleic acid sequence and the second nucleic acid sequence are included on a single vector. In other embodiments, the first nucleic acid sequence and the second nucleic acid sequence are located on separate vectors.

In another aspect, the present invention provides a recombinant cell line that includes a host cell transfected with an expression system. In some embodiments, the expression system is contained within a single vector. In other embodiments, the expression system is contained among two or more vectors so that the host cell is co-transfected with all of the vectors of the expression system to obtain the recombinant cell line. In one embodiment, the host cell is a Namalwa cell.

In another aspect, the present invention provides a TLR agonist identified using either an expression system or a recombinant cell line according to the present invention.

In yet another aspect, the present invention provides pharmaceutical compositions including a TLR agonist identified using either an expression system or a recombinant cell line according to the present invention.

Various other features and advantages of the present invention should become readily apparent with reference to the following detailed description, examples, and appended claims. In several places throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

Detailed Description of Illustrative Embodiments of the Invention

The present invention provides gene expression systems and recombinant cell lines that may be useful for detecting TLR activation based on detecting induction of a downstream cellular response to TLR activation (e.g., production or secretion of one or more immune system compounds such as cytokines or co-stimulatory markers) rather than NF-κB activation. In some cases, the cellular response may be mediated by NF-κB, but in other cases the cellular response may be NF-κB-independent. Thus, the present invention provides gene expression systems and recombinant cell lines that may be useful for detecting a broader range of TLR activation than is possible by monitoring NF-κB activation. This may provide an ability to identify certain TLR agonists that would not be detected using an assay based on NF-κB activation. The gene expression systems and recombinant cell lines of the present invention also may provide a more relevant indication of the quantitative character of a particular cellular response to TLR activation by a particular TLR agonist.

In some cases, a gene expression system or recombinant cell line according to the present invention may be useful for detecting TLR activation that is not accompanied by NF-κB activation. Accordingly, the gene expression system and recombinant cell line may be employed to identify TLR agonists that do not necessarily also activate NF-κB. Such TLR agonists may be useful for treatment or prevention of certain conditions in which the production and secretion of pro-inflammatory cytokines such as those induced by NF-κB activation may be undesirable.

For purposes of this invention, the following terms shall have the meanings set forth.

"Activation" refers to modifying the indicated protein so that the protein provides a biological function. For example, TLR activation refers to modifying a TLR - for example, a conformational modification such as in response to exposure of the TLR to an agonist - so that the TLR is capable of inducing the production and secretion of certain cytokines.

"Agonist" refers to a compound that can combine with a receptor (e.g., a TLR) to produce a cellular response. An agonist may be a ligand that directly binds to the receptor. Alternatively, an agonist may combine with a receptor indirectly by, e.g., (a) forming a complex with another molecule that directly binds to the receptor, or (b) otherwise results in the modification of another compound so that the other compound directly binds to the receptor. An agonist may be referred to as an agonist of a particular TLR (e.g., a TLR6 agonist).

"Amino acid sequence" refers to a particular ordered sequence of amino acids, whether naturally occurring or engineered.

"Co-transfect" and variations thereof refer to transfecting a host cell with more than one vector. A host cell may be co-transfected by transfecting with two or more vectors one at a time or in any convenient combination of vectors, including simultaneous transfection with all vectors.

"Express" and variations thereof refer to the ability of a cell to transcribe a structural gene to mRNA, then translate the mRNA to synthesize a protein that provides a detectable biological or biochemical function. "Expressible" refers to the ability of a particular nucleic acid sequence to be expressed by a cell that contains the nucleic acid sequence.

"Immune system compound" refers to any compound that is produced or secreted by cells of the immune system in response to an immunological challenge. Immune system compounds include but are not limited to cytokines, chemokines, co-stimulatory markers, and defensins.

"IRM compound" refers to a compound that alters the level of one or more immune system compounds when administered to an IRM-responsive cell. Representative IRM compounds include the small organic molecules, purine derivatives, small heterocyclic compounds, amide derivatives, and oligonucleotide sequences described above.

"Nucleic acid sequence" refers generally to a region of DNA that has a definable function such as (a) encoding a peptide, polypeptide, or protein or (b) controlling expression of a nucleic acid sequence that encodes a peptide, polypeptide, or protein. For example, a nucleic acid sequence that encodes TLR6 refers generically to any sequence of nucleotides that encodes a TLR6 protein, without regard to (a) the species source of the nucleic acid sequence, (b) specific nucleotide sequence variants, or (c) whether such nucleotide sequence variants are naturally occurring or engineered.

"Nucleotide sequence" refers to a particular ordered sequence of nucleotide bases, whether naturally occurring or engineered.

It has been found that induction of certain secreted proteins or polypeptides can be useful as reporters of TLR activation. For example, IFN-α is a cytokine secreted by such immune system cells as T lymphocytes, macrophages, plasmacytoid monocytes, dendritic cells, and natural killer cells. IFN-α is involved in regulating a host's innate and adaptive immune responses to an immunological challenge, perhaps by providing a link between the two responses [Brassard *et al.*, *Journal of Leukocyte Biology* 71: 565-581 (2002)]. The innate immune response can include the cell-mediated response of natural killer (NK) cells to a non-self (e.g., neoplastic) or foreign (e.g., viral) antigen. IFN-α also may indirectly regulate the balance between Th1 and Th2 cell populations and, therefore, the innate and adaptive immune responses. Moreover, induction of IFN-α is independent of NF-κB activation.

Additionally, the production and secretion of NF-κB-dependent cytokines can be useful as reporters of cellular responses resulting from immunological challenge. Detection and measurement of such cytokines may provide comparative qualitative data regarding a cell's response to immunological challenge that is more relevant to an investigator than NF-κB activation data.

Thus, in certain embodiments, the present invention relates to recombinant cell lines and gene expression systems designed to assist detecting induction of immune system compounds and identification of compounds that induce expression of immune system compounds through TLRs.

Parts of the following description are provided in the context of IFN-α induction and detection. However, many of the features of the embodiments described below also may be realized using expression systems and recombinant cell lines designed to

specifically detect or induce other immune system compounds. Thus, expression systems and recombinant cell lines designed to specifically detect or induce immune system compounds other than IFN-α are explicitly included in the scope of the present invention.

The present invention provides a recombinant cell line capable of inducing gene expression from an expression control sequence of a gene that encodes an immune system compound (e.g., IFN-α) in response to TLR activation. In some embodiments, for example, cells of the recombinant cell line, when exposed to a TLR agonist, can induce expression from an IFN-α promoter to a greater extent than cells of the corresponding untransfected cell line. Cells of the untransfected cell lines may substantially lack a functional level of TLR expression (i.e., untransfected cells may not detectably induce expression from the IFN-α promoter in response to exposure to a TLR agonist). Alternatively, cells of the untransfected cell line may exhibit a baseline level of background TLR function, but the baseline level is less than the level of TLR function observed in cells of the corresponding recombinant (i.e., transfected) cell line.

Cells of the recombinant cell lines include a first nucleic acid sequence that encodes a TLR operably linked to an expression control sequence. The cells also include a second nucleic acid sequence that encodes a reporter capable of generating a detectable signal when it is expressed in the recombinant cell under conditions suitable for generating the detectable signal. The reporter is linked to a second expression control sequence that is capable of being induced by activation of the TLR encoded by the first nucleic acid sequence.

The TLR encoded by the first nucleic acid sequence may be any TLR. Ten different human TLRs have been identified, cloned, and sequenced. TLRs also are known to exist in other mammals including, for example, mice and chimpanzees. The nucleotide sequences of the ten human TLRs and many non-human TLRs are known, have been published, and are readily accessible from various sequence databases including GenBank. The first nucleic acid sequence may include the nucleotide sequence of any one of the TLRs, whether human or non-human. In one embodiment, the TLR is human TLR6; in another embodiment, the TLR is human TLR7. Alternatively, the first nucleic acid may encode any one of the ten human TLRs, any non-human TLR, or any combination of two or more TLRs that may be desirable for a particular construct.

The first nucleic acid sequence can include a nucleotide sequence that differs from a specific published nucleotide sequence for the TLR encoded by the first nucleic acid sequence. For example, the first nucleic acid sequence can contain one or more substitutions (compared to a published TLR nucleotide sequence) that do not alter the amino acid sequence of the TLR protein expressed from the first nucleic acid sequence. Such a substitution may be termed a degenerate substitution. Nucleotide sequences containing one or more degenerate substitutions compared to a known TLR nucleotide sequence are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

As another example, certain nucleotide substitutions may alter the amino acid sequence of the TLR protein. For certain amino acid substitutions, however, the chemical properties of the protein having the altered amino acid sequence are similar to the chemical properties of the protein having the native amino acid sequence. Amino acids may be divided into four groups based on the chemical characteristics of the amino acid side groups: neutral, non-polar amino acids include glycine, alanine, valine, isoleucine, leucine, phenylalanine, proline, and methionine; neutral, polar amino acids include serine, threonine, tyrosine, tryptophan, asparagine, glutamine, and cysteine; acidic amino acids include aspartic acid and glutamic acid; and basic amino acids include lysine, arginine, and histidine. Substitution of one amino acid for another amino acid within the same group may have little or no functional effect on the resulting protein because of the similarity of the chemical characteristics of the amino acids involved in the substitution. Such amino acid substitutions may be termed a conservative amino acid substitution. Nucleotide sequences that, when compared to a known TLR nucleotide sequence, generate one or more conservative amino acid substitutions are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

The nucleic acid that encodes a TLR may be cloned into an expression vector so that it is under the expression control of its own promoter, a homologous TLR promoter, or any heterologous promoter inducible in an appropriate host cell. For example, in certain embodiments, the TLR6 structural gene may be cloned into the commercially available mammalian expression vector pCI-neo. In this case, the TLR6 structural gene may be cloned into the vector's cloning region using the NheI and MluI restrictions sites. In such an embodiment, after transfection of the vector into a mammalian cell, the TLR6

structural gene is under the transcriptional control of the vector's CMV enhancer/promoter region.

The second nucleic acid sequence encodes a reporter that is capable of generating a detectable signal when expressed in a host cell under conditions appropriate for generating the desired detectable signal. A wide variety of suitable reporter systems are known. For example, luciferase gene expression may generate a detectable luminescent signal under appropriate conditions. As another example, β-galactosidase expression can generate a detectable color change under appropriate conditions. As yet another example, production and secretion of an immune system compound may be detected by an enzyme-linked immunosorbent assay (ELISA). These and other reporter systems are known and assays for generating the detectable signals are commercially available.

The second nucleic acid sequence is operably linked to a second expression control sequence that includes a promoter sequence selected to be inducible by activation of the TLR encoded by the first nucleic acid sequence. Thus, expression and activation of the TLR encoded by the first nucleic acid sequence will induce gene expression from the second expression control sequence, thereby causing expression of the reporter, which may be detected by performing an assay designed to detect expression of the reporter. The second expression control sequence may include any suitable nucleotide sequence that can induce expression (e.g., a promoter) of a structural gene upon activation of the TLR encoded by the first nucleic acid sequence. Nucleotide sequences suitable for use as second expression control sequences include promoter sequences of TLR-inducible genes including but not limited to genes encoding cytokines, chemokines, co-stimulatory markers, and defensins. In certain embodiments, the second expression control sequence can include an IFN-α1 promoter. When the reporter system being employed to detect TLR activation includes detecting production and secretion of an immune system compound with an appropriate ELISA assay, the second expression control sequence may include the promoter of the gene encoding the immune system compounds being expressed and detected as the reporter. However, in certain embodiments, it may be desirable to express the immune system compound from a heterologous promoter.

The first nucleic acid sequence and the second nucleic acid sequence may be contained within a single vector. Alternatively, the first nucleic acid sequence and the second nucleic acid sequence may be on separate vectors and co-transfected into a suitable

host cell. In certain embodiments, for example, the first nucleic acid sequence may be cloned into the pCI-neo vector as described above, while the second nucleic acid sequence can be cloned into a reporter vector. One example of a commercially available reporter vector is the pGL3-Enhancer vector, which includes a luciferase reporter gene downstream of a cloning site for cloning a promoter sequence of interest. In some embodiments, the promoter of a TLR-inducible immune system compound may be cloned into the pGL3-Enhancer cloning site. In one such embodiment, the IFN-α promoter may be cloned into the pGL3-Enhancer cloning site.

Suitable host cells include any transfectable cells capable of expressing exogenous mammalian genes. In some embodiments, the host cells may be mammalian cells such as human cells or mouse cells. For example, suitable host cells include human cells or descendants of a human cell including but not limited to Namalwa cells or HEK293 cells. Alternatively, the host cells may be mouse cells or descendants of a mouse cell including but not limited to RAW 264.7 cells.

In one embodiment, the host cells include Namalwa cells. Namalwa cells have certain characteristics that may be particularly desirable for certain embodiments of the present invention. For example, Namalwa cells can include an expressible chromosomal IFN-α gene locus. Thus, upon appropriate stimulation (e.g., viral infection), Namalwa cells can be induced to produce and secrete IFN-α from the chromosomal IFN-α gene locus. However, Namalwa cells do not naturally express certain TLRs (e.g., TLR6, TLR7, or TLR9). Certain agonists of such TLRs have been shown to induce IFN-α expression in other cell types (e.g., PMBCs), but may not induce IFN-α expression in Namalwa cells unless a functional level of TLR expression is provided.

Namalwa cells transfected with an expression system according to the present invention may be capable of expressing a functional level of the TLR provided by the expression system. Thus, Namalwa cells transfected with an expression system according to certain embodiments of the present invention may inducibly express IFN-α as a result of activating the cloned TLR (e.g., by exposure of the transfected Namalwa cells to an agonist). Thus, certain transfected cell lines of the present invention provide an ability to detect a TLR agonist by detecting TLR-mediated IFN-α expression by Namalwa cells. Such IFN-α expression may occur from the chromosomal IFN-α gene or from an IFN-α promoter cloned into the reporter vector.

Namalwa cells transfected with an expression system according to certain embodiments of the present invention can provide alternative means of detecting TLR expression. First, transfected Namalwa cells may generate a detectable signal as a result of expressing the reporter from the second expression control sequence, which may or may not include an IFN-α promoter (see Table 2). Second, transfected Namalwa cells may produce and secrete IFN-α from the chromosomal IFN-α gene locus. A transfected Namalwa cell line according to the present invention may be used to screen compounds in order to identify those compounds that induce TLR expression, i.e., TLR agonists.

Therefore, the present invention also provides TLR agonist compounds identified using an expression system or a recombinant cell line according to certain embodiments of the present invention. As described above, the expression systems and recombinant cell lines may provide the ability to identify TLR activation that may not be detectable using previously known TLR activation assays. A compound that induces TLR activity detectable by using a gene expression system or a recombinant cell line according to the present invention may be considered a TLR agonist. Such TLR agonists may include chemical structures similar in certain respects to the chemical structures of known IRM compounds. Alternatively, a gene expression system or a recombinant cell line according to the present invention may provide a tool for the screening (e.g., high throughput screening) chemically diverse compounds that may lead to the discovery of new TLR agonists, some of which may contain new chemical core structures capable of activating TLRs.

The present invention also provides pharmaceutical compositions containing a TLR agonist identified using an expression system or a recombinant cell line according to the present invention, or a pharmaceutically acceptable salt thereof, in an amount effective for inducing a TLR-mediated cellular response.

Examples

The following examples have been selected merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however, that while the examples serve this purpose, the particular materials and amounts used as well as other conditions and details are not to be construed in a matter that would unduly limit the scope of this invention.

Construction of vectors

The vector pIFN-α1-luc was constructed by inserting BglII sites at both ends of the human IFN-α1 promoter (SEQ ID NO:21). The BglII sites were inserted into the IFN-α1 promoter and the sequence was amplified using the primer pair of SEQ ID NO:22 and SEQ ID NO:23. The amplified IFN-α1 promoter was cloned into the pGL3-Enhancing vector (Promega Corp., Madison, WI) at its BglII site.

The vector pCI-TLR6 was constructed by inserting SEQ ID NO:11 (GenBank Accession No. NM 006068), which includes the human TLR6 coding sequence, into the pCI-neo mammalian expression vector (Promega Corp.) at the vector's NheI and MluI restriction sites.

Transfections

Unless otherwise indicated, all incubations were performed at 37°C with 5% CO_2 at 98% humidity.

Culture medium was prepared from complete RPMI 1640 medium (BioSource International, Inc., Camarillo, CA). Fetal bovine serum (Atlas Biologicals, Inc., Ft. Collins, CO) was added to a final concentration of 7.5% (vol/vol); L-glutamine (BioSource International, Inc.) was added to 5 mM; and sodium pyruvate (BioSource International, Inc.) was added to 1 mM.

Burkitt's Lymphoma lymphoblastoid Namalwa cells (ATCC Accession No. CRL-1432) were grown by incubation in culture medium overnight. Cells were harvested by centrifugation in a tabletop centrifuge (1200 RPM for 5 minutes), and then resuspended in phosphate buffered sucrose to a concentration of 1.3×10^7 cells per milliliter.

For each transfection, a 750 μL aliquot of the cell suspension was placed in an electroporation cuvette with 4 mm gaps. 10 μg of the pIFN-α1-luc vector and 10 μg of the pCI-TLR6 vector were added to the electroporation cuvette. The cell and vector mixtures were incubated at room temperature for 5 minutes. The cells were electroporated using a BioRad Gene Pulser (BioRad Laboratories, Hercules, CA) set to at 500 μF capacitance and 0.27 volts, then incubated at room temperature for 5 minutes.

The electroporated cells were suspended in 10 mLs of culture medium and incubated overnight. Dead cells and debris were removed after 24 hours using a MACS

Dead Cell Removal kit (Miltenyi Biotec, Auburn, CA). Cells were resuspended in 10 mLs of culture medium and incubated for an additional 24 hours.

Transfected cells were selected by adding G418 (Promega Corp., Madison, WI) to a final concentration of 1 mg/mL and incubating the cells for seven days.

Assays

The selected transfected cells were counted and resuspended to a concentration of 1×10^6 cell per mL in culture medium. 100 μl aliquots of cells were placed in the wells of a white-walled, white-bottomed 96-well plate (Corning, Inc. Corning, NY). 1.0 μL of an IRM compound from Table 1 (prepared at 1 mM in 100% DMSO) was added to some cell aliquots so that the final concentration of IRM compound was 10 μM. As a positive control, some cell aliquots were incubated with Sendai virus instead of IRM compound. As a negative control, some cell aliquots were incubated with DMSO without IRM compound. In all cases, the cells were incubated for 18 hours.

Table 1 - IRM Compounds

Compound	Chemical Name	Citation
IRM 1	4-amino-2-ethoxymethyl-α,α-dimethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol	U.S. 5,352,784 Example 91
IRM 2	4-amino-α,α,2-trimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol	U.S. 5,266,575 Example C1
IRM 3	N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide	U.S. 6,331,539 Example 6
IRM 4	1-{2-[3-(3-pyridyl)propoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine	WO 02/46193 Example 33
IRM 5	2-butyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine	U.S. 6,194,425 Example 39
IRM 6	2-butyl-6,7,8,9-tetrahydro-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine	U.S. 6,194,425 Example 40
IRM 7	N^3-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-6-(1*H*-1-pyrrolyl)nicotinamide	U.S. 6,451,810 Example 60
IRM 8	2-ethyl-1-[5-(methylsulfonyl)pentyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine	WO 02/46192 Example 13

The plates were equilibrated to room temperature before 1 volume of reconstituted LucLight Plus (Packard Instruments, Meriden, CT) was added to each aliquot of cells. Each well of the plate was read on an LJL Analyst (LJL Biosystems, Inc., Sunnyvale, CA) set with a 5 minute dark adapt. Data from a representative experiment are shown in Table 2. The data are expressed as the fold increase in luciferase induction off of the IFN-α1 promoter in cell aliquots incubated with the indicated stimulant compared to the negative control in which the cell aliquots were incubated with only DMSO.

Table 2 - TLR Expression by pIFN-α1-luc/pCI-TLR6 Co-Transfected Namalwa cells

Stimulant	Fold Increase in Luciferase Induction
IRM1	3.6
IRM2	2.7
IRM3	2.6
IRM4	4.0
IRM5	3.2
IRM6	2.9
IRM7	3.2
IRM8	2.3
Sendai virus	2.7

The complete disclosures of the patents, patent documents and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. In case of conflict, the present specification, including definitions, shall control.

Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. Illustrative embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

What is Claimed is:

1. An expression system comprising:

a first nucleic acid sequence that encodes a Toll-like receptor operably linked to a first expression control sequence; and

a second nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter.

2. The expression system of claim 1 wherein the second expression control sequence comprises an IFN-α promoter.

3. The expression system of claim 1 wherein the first nucleic acid sequence comprises the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, or a degenerate variant of any of the foregoing.

4. The expression system of claim 1 wherein the first nucleic acid sequence comprises a nucleotide sequence that encodes a polypeptide having the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, or any one of the foregoing sequences with one or more conservative amino acid substitutions.

5. The expression system of claim 1 wherein the detectable signal comprises luciferase activity or β-galactosidase activity.

6. The expression system of claim 1 wherein a first vector comprises the first nucleic acid sequence and a second vector comprises the second nucleic acid sequence.

7. A vector comprising the expression system of claim 1.

8. A TLR agonist identified using the expression system of claim 1.

9. A pharmaceutical composition comprising the TLR agonist of claim 8, or a pharmaceutically acceptable salt thereof.

10. A cultured cell comprising the expression system of claim 1.

11. The cultured cell of claim 10 wherein the cell is a mammalian cell or a descendent of a mammalian cell.

12. The culture cell of claim 11 wherein the cell is a human cell or a descendent of a human cell.

13. The cultured cell of claim 10 further comprising an expressible nucleic acid sequence that encodes IFN-α operably linked to a third expression control sequence.

14. The cultured cell of claim 13 wherein the expressible nucleic acid sequence that encodes IFN-α is located on a chromosome of the cultured cell.

15. The cultured cell of claim 14 wherein the cultured cell is a Namalwa cell.

16. The cultured cell of claim 13 wherein the expressible nucleic acid sequence that encodes IFN-α is located on an extrachromosomal vector.

17. A TLR agonist identified using the cultured cell of claim 10.

18. A pharmaceutical composition comprising the TLR agonist of claim 17, or a pharmaceutically acceptable salt thereof.

58182US002.ST25.txt
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Ghosh, Tarun K.
Fink, Jason R.

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Glu Val Ala Asp Cys Ser His Leu Lys Leu Thr Gln Val Pro Asp Asp
35 40 45

Leu Pro Thr Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu Arg
50 55 60

Arg Leu Pro Ala Ala Asn Phe Thr Arg Tyr Ser Gln Leu Thr Ser Leu
65 70 75 80

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Asp Val Gly Phe Asn Thr Ile Ser Lys Leu Glu Pro Glu Leu Cys Gln
                85                  90                  95

Lys Leu Pro Met Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu Ser
            100                 105                 110

Gln Leu Ser Asp Lys Thr Phe Ala Phe Cys Thr Asn Leu Thr Glu Leu
        115                 120                 125

His Leu Met Ser Asn Ser Ile Gln Lys Ile Lys Asn Asn Pro Phe Val
    130                 135                 140

Lys Gln Lys Asn Leu Ile Thr Leu Asp Leu Ser His Asn Gly Leu Ser
145                 150                 155                 160

Ser Thr Lys Leu Gly Thr Gln Val Gln Leu Glu Asn Leu Gln Glu Leu
                165                 170                 175

Leu Leu Ser Asn Asn Lys Ile Gln Ala Leu Lys Ser Glu Glu Leu Asp
            180                 185                 190

Ile Phe Ala Asn Ser Ser Leu Lys Lys Leu Glu Leu Ser Ser Asn Gln
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Ile Lys Glu Phe Ser Pro Gly Cys Phe His Ala Ile Gly Arg Leu Phe
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Gly Leu Phe Leu Asn Asn Val Gln Leu Gly Pro Ser Leu Thr Glu Lys
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Leu Cys Leu Glu Leu Ala Asn Thr Ser Ile Arg Asn Leu Ser Leu Ser
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Asn Ser Gln Leu Ser Thr Thr Ser Asn Thr Thr Phe Leu Gly Leu Lys
            260                 265                 270

Trp Thr Asn Leu Thr Met Leu Asp Leu Ser Tyr Asn Asn Leu Asn Val
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Val Gly Asn Asp Ser Phe Ala Trp Leu Pro Gln Leu Glu Tyr Phe Phe
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Leu Glu Tyr Asn Asn Ile Gln His Leu Phe Ser His Ser Leu His Gly
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Leu Phe Asn Val Arg Tyr Leu Asn Leu Lys Arg Ser Phe Thr Lys Gln
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Ser Ile Ser Leu Ala Ser Leu Pro Lys Ile Asp Asp Phe Ser Phe Gln
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Trp Leu Lys Cys Leu Glu His Leu Asn Met Glu Asp Asn Asp Ile Pro
355 360 365

Gly Ile Lys Ser Asn Met Phe Thr Gly Leu Ile Asn Leu Lys Tyr Leu
370 375 380

Ser Leu Ser Asn Ser Phe Thr Ser Leu Arg Thr Leu Thr Asn Glu Thr
385 390 395 400

Phe Val Ser Leu Ala His Ser Pro Leu His Ile Leu Asn Leu Thr Lys
405 410 415

Asn Lys Ile Ser Lys Ile Glu Ser Asp Ala Phe Ser Trp Leu Gly His
420 425 430

Leu Glu Val Leu Asp Leu Gly Leu Asn Glu Ile Gly Gln Glu Leu Thr
435 440 445

Gly Gln Glu Trp Arg Gly Leu Glu Asn Ile Phe Glu Ile Tyr Leu Ser
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Tyr Asn Lys Tyr Leu Gln Leu Thr Arg Asn Ser Phe Ala Leu Val Pro
465 470 475 480

Ser Leu Gln Arg Leu Met Leu Arg Arg Val Ala Leu Lys Asn Val Asp
485 490 495

Ser Ser Pro Ser Pro Phe Gln Pro Leu Arg Asn Leu Thr Ile Leu Asp
500 505 510

Leu Ser Asn Asn Asn Ile Ala Asn Ile Asn Asp Asp Met Leu Glu Gly
515 520 525

Leu Glu Lys Leu Glu Ile Leu Asp Leu Gln His Asn Asn Leu Ala Arg
530 535 540

Leu Trp Lys His Ala Asn Pro Gly Gly Pro Ile Tyr Phe Leu Lys Gly
545 550 555 560

Leu Ser His Leu His Ile Leu Asn Leu Glu Ser Asn Gly Phe Asp Glu
565 570 575

Ile Pro Val Glu Val Phe Lys Asp Leu Phe Glu Leu Lys Ile Ile Asp
580 585 590

Leu Gly Leu Asn Asn Leu Asn Thr Leu Pro Ala Ser Val Phe Asn Asn
595 600 605

Gln Val Ser Leu Lys Ser Leu Asn Leu Gln Lys Asn Leu Ile Thr Ser
610 615 620

Val Glu Lys Lys Val Phe Gly Pro Ala Phe Arg Asn Leu Thr Glu Leu
625 630 635 640

Asp Met Arg Phe Asn Pro Phe Asp Cys Thr Cys Glu Ser Ile Ala Trp
645 650 655

Phe Val Asn Trp Ile Asn Glu Thr His Thr Asn Ile Pro Glu Leu Ser
660 665 670

Ser His Tyr Leu Cys Asn Thr Pro Pro His Tyr His Gly Phe Pro Val
675 680 685

Arg Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu Leu
690 695 700

Phe Phe Met Ile Asn Thr Ser Ile Leu Leu Ile Phe Ile Phe Ile Val
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Leu Leu Ile His Phe Glu Gly Trp Arg Ile Ser Phe Tyr Trp Asn Val
725 730 735

Ser Val His Arg Val Leu Gly Phe Lys Glu Ile Asp Arg Gln Thr Glu
740 745 750

Gln Phe Glu Tyr Ala Ala Tyr Ile Ile His Ala Tyr Lys Asp Lys Asp
755 760 765

Trp Val Trp Glu His Phe Ser Ser Met Glu Lys Glu Asp Gln Ser Leu
770 775 780

Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Phe Glu Leu
785 790 795 800

Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe Val
805 810 815

Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Lys Arg Phe Lys Val
820 825 830

His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile Ile
835 840 845

Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu
850 855 860

Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro
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Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu Ser Arg Cys
35 40 45

Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu
50 55 60

Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly
65 70 75 80

Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr
85 90 95

Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu
100 105 110

Lys Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe Lys Leu Pro
115 120 125

Glu Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp Leu Ser Ser
130 135 140

Asn Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val Leu His Gln
145 150 155 160

Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn
165 170 175

Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr
180 185 190

Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln
195 200 205

Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg
210 215 220

Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu
225 230 235 240

Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr
245 250 255

Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser
260 265 270

Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr
275 280 285

Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln
290 295 300

Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser
305 310 315 320

Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu
325 330 335

Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser
340 345 350

Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe

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Glu His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe
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Ser Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His
                405                 410                 415

Thr His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser
            420                 425                 430

Leu Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu
        435                 440                 445

Pro Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser
    450                 455                 460

Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser
465                 470                 475                 480

Ser Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp
                485                 490                 495

Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser
            500                 505                 510

Leu Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro
        515                 520                 525

Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr
    530                 535                 540

Cys Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu
545                 550                 555                 560

Leu Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln
                565                 570                 575

Gly Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr
            580                 585                 590

Ile Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala
        595                 600                 605
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Val Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu Ala Gly Cys
610 615 620

Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr
625 630 635 640

Ser Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu
645 650 655

Glu Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe
660 665 670

Ile Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His
675 680 685

Lys Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser
690 695 700

Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu
705 710 715 720

Ser Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys
725 730 735

Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn
740 745 750

Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp
755 760 765

Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu
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Gly Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile
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aactccaaca ggctgacagt tctttctcac aatgatttac ctgctaattt agagatcctg 180

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Glu Pro Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser Lys
35 40 45

Asp Phe Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr Gln
50 55 60

Tyr Ser Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp Phe
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Val Pro Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp Asn
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Ser Arg Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp Gly
            100                 105                 110

Trp Cys Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser Asp
        115                 120                 125

Leu Asn Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln Tyr
    130                 135                 140

Gln Leu Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln Gln
145                 150                 155                 160

Tyr Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu His
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Lys Leu Ser Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys Asp
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Asn Asn Ile Pro Leu Gln Thr Val Ala Thr Ile Ser
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Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile
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Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val
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Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe
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Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu
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Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu
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Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn
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Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys
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Phe Leu Ser Glu Leu Thr Arg Gly Ser Thr Leu Leu Asn Phe Thr Leu
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Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe Gln Phe
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Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile
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Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu
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Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser
305                 310                 315                 320

Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu
                325                 330                 335

Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro
            340                 345                 350

Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser
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Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu Ile Leu
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Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys
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Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu
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Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val
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Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser
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Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp
        515                 520                 525

Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys Asn Ile
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Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys
545                 550                 555                 560

Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His
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Met Ser Glu Leu Ser Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Gly
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Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr
        595                 600                 605

Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr
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Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu
625                 630                 635                 640

Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val
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Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys
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Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile
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Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro
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Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His
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His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu
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Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys
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Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser
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Lys Arg Gly Leu Phe Trp Ala Asn Ile Arg Ala Ala Phe Asn Met Lys
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Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe
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Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
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Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr
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Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
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Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile
145 150 155 160

Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
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Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
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Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
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Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro
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Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
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Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu
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His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu
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Leu Gln Val Tyr Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser
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Leu Lys Ser Leu Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu
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Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu
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Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met
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Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys
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Ile Ser Pro Ser Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala
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Glu Ala Ser Phe Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln
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Thr Leu Asp Leu Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp
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Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu
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Ile Ser Gln Thr Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu
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Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr
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Ala Phe Glu Glu Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn
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Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr
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Lys Asn Leu Lys Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile
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Arg Tyr Leu Gln Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp
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Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys
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Ser Phe Ser Trp Lys Lys Leu Gln Cys Leu Lys Asn Leu Glu Thr Leu
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<400> 16

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Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu
        35   40   45

Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr
    50   55   60

Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn
65   70   75   80

Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His
                85   90   95

Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn
            100   105   110

Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg
        115   120   125

Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu
    130   135   140

58182US002.ST25.txt

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Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr
                165                 170                 175

Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile
            180                 185                 190

Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu
        195                 200                 205

Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu
    210                 215                 220

Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu
225                 230                 235                 240

Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn
                245                 250                 255

Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly
            260                 265                 270

Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln
        275                 280                 285

Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala
    290                 295                 300

Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe
305                 310                 315                 320

Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu
                325                 330                 335

Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser
            340                 345                 350

Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser
        355                 360                 365

Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu
    370                 375                 380

Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn
385                 390                 395                 400
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Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn
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Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro
            420                 425                 430

Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln
        435                 440                 445

Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His
    450                 455                 460

Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala
465                 470                 475                 480

Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile
                485                 490                 495

Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu Asn Leu
            500                 505                 510

Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe Ser Ala
        515                 520                 525

Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu Asp Phe
    530                 535                 540

Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val Leu Asp
545                 550                 555                 560

Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr His His
                565                 570                 575

Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn Leu Ser
            580                 585                 590

His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu Ser Lys
        595                 600                 605

Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp
    610                 615                 620

Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu Lys Asn
625                 630                 635                 640

Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn
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Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His Ile Asn
660 665 670

Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln Phe Pro
675 680 685

Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe Leu Thr
690 695 700

Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu Leu Ser
705 710 715 720

His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu Val Ser
725 730 735

Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr Ile Asn
740 745 750

Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met Leu Glu
755 760 765

Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp Phe Arg
770 775 780

Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu Val Asp
785 790 795 800

Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser
805 810 815

Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile Leu Phe
820 825 830

Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala
835 840 845

His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu
850 855 860

Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr
865 870 875 880

Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr Asp Trp
885 890 895

Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp Lys Asn
900 905 910

Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile
915 920 925

Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe
930 935 940

Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe
945 950 955 960

Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile
965 970 975

Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu
980 985 990

Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro
995 1000 1005

Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn Val Val Leu
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Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met Tyr Val Asp Ser Ile
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<400> 18

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35 40 45

Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
50 55 60

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
65 70 75 80

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
85 90 95

Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met
100 105 110

Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
115 120 125

Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser
130 135 140

Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser
145 150 155 160

Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly
165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro
180 185 190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
195 200 205

Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr
210 215 220

Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu
225 230 235 240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
245 250 255

Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe
260 265 270

Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
275 280 285

Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe
290 295 300

Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu
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Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu
325 330 335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala
340 345 350

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His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu
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Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu
    370                 375                 380

Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met
385                 390                 395                 400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly
                405                 410                 415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu
            420                 425                 430

Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu
        435                 440                 445

Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu
    450                 455                 460

Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser
465                 470                 475                 480

Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
                485                 490                 495

His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val
            500                 505                 510

Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu
        515                 520                 525

Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu
    530                 535                 540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly
545                 550                 555                 560

Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr
                565                 570                 575

Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser
            580                 585                 590

Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn
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58182US002.ST25.txt

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Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe
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Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu
625 630 635 640

His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln
645 650 655

Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser
660 665 670

Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg
675 680 685

Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg
690 695 700

Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe
705 710 715 720

Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
725 730 735

Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu
740 745 750

Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
755 760 765

Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu
770 775 780

Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser
785 790 795 800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
805 810 815

Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val
820 825 830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
835 840 845

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Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp
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Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln
865                 870                 875                 880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu
                885                 890                 895

Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp
            900                 905                 910

Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr
        915                 920                 925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
    930                 935                 940

Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945                 950                 955                 960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg
                965                 970                 975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
            980                 985                 990

Leu Leu Trp Pro His Gln Pro Ser  Gly Gln Arg Ser Phe  Trp Ala Gln
        995                 1000                1005

Leu Gly  Met Ala Leu Thr Arg  Asp Asn His His Phe  Tyr Asn Arg
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Asn Phe  Cys Gln Gly Pro Thr  Ala Glu
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<212> DNA
<213> Homo sapiens

<400> 19

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Ala Thr Thr Thr Leu Asp Leu Ser Tyr Asn Leu Leu Phe Gln Leu Gln
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Ser Ser Asp Phe His Ser Val Ser Lys Leu Arg Val Leu Ile Leu Cys
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His Asn Arg Ile Gln Gln Leu Asp Leu Lys Thr Phe Glu Phe Asn Lys
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Glu Leu Arg Tyr Leu Asp Leu Ser Asn Asn Arg Leu Lys Ser Val Thr

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Trp Tyr Leu Leu Ala Gly Leu Arg Tyr Leu Asp Leu Ser Phe Asn Asp
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Phe Asp Thr Met Pro Ile Cys Glu Glu Ala Gly Asn Met Ser His Leu
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Lys Ile Ala His Leu His Leu Asn Thr Val Phe Leu Gly Phe Arg Thr
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Leu Pro His Tyr Glu Glu Gly Ser Leu Pro Ile Leu Asn Thr Thr Lys
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Leu His Ile Val Leu Pro Met Asp Thr Asn Phe Trp Val Leu Leu Arg
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Asp Gly Ile Lys Thr Ser Lys Ile Leu Glu Met Thr Asn Ile Asp Gly
210 215 220

Lys Ser Gln Phe Val Ser Tyr Glu Met Gln Arg Asn Leu Ser Leu Glu
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Asn Ala Lys Thr Ser Val Leu Leu Leu Asn Lys Val Asp Leu Leu Trp
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Asp Asp Leu Phe Leu Ile Leu Gln Phe Val Trp His Thr Ser Val Glu
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His Phe Gln Ile Arg Asn Val Thr Phe Gly Gly Lys Ala Tyr Leu Asp
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His Asn Ser Phe Asp Tyr Ser Asn Thr Val Met Arg Thr Ile Lys Leu
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Glu His Val His Phe Arg Val Phe Tyr Ile Gln Gln Asp Lys Ile Tyr
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Leu Leu Leu Thr Lys Met Asp Ile Glu Asn Leu Thr Ile Ser Asn Ala
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Gln Met Pro His Met Leu Phe Pro Asn Tyr Pro Thr Lys Phe Gln Tyr
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His Leu Asp Leu Ser Gln Asn Leu Leu Gln His Lys Asn Asp Glu Asn
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Asp Leu Asn Asn Asn Gln Ile Gln Thr Val Pro Lys Glu Thr Ile His
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Glu Leu Lys Asn Phe Ile Gln Leu Glu Thr Tyr Ser Glu Val Met Met
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Val Gly Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg
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Gly Ile Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr
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Ala Leu Leu Ile Val Thr Ile Val Val Ile Met Leu Val Leu Gly Leu
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Glu Lys Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe
660 665 670

Asp Pro Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys
675 680 685

Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu
690 695 700

Trp Cys His Tyr Glu Phe Tyr Phe Ala His His Asn Leu Phe His Glu
705 710 715 720

Asn Ser Asp His Ile Ile Leu Ile Leu Leu Glu Pro Ile Pro Phe Tyr
725 730 735

Cys Ile Pro Thr Arg Tyr His Lys Leu Lys Ala Leu Leu Glu Lys Lys
740 745 750

Ala Tyr Leu Glu Trp Pro Lys Asp Arg Arg Lys Cys Gly Leu Phe Trp
755 760 765

Ala Asn Leu Arg Ala Ala Ile Asn Val Asn Val Leu Ala Thr Arg Glu
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